

REMARKS

I. Introduction

In response to the Office Action dated July 31, 2003, claims 9, 10, and 14 have been amended and claim 11 has been cancelled. Claims 9-10 and 12-16 remain in the application. Re-examination and re-consideration of the application, as amended, is requested.

II. Claim Amendments

Applicants' attorney has made amendments to the claims as indicated above. These amendments were made solely for the purpose of clarifying the language of the claims, and were not required to distinguish the claims over the prior art.

III. Examiner Interview Summary

Record is made of a telephone interview on October 27, 2003 between Applicants' attorney William Wood and Examiner Roy R. Teller in connection with the present patent application.

Applicants' Attorney wishes to thank Examiner Teller for his very helpful suggestions regarding clarifying language for the claims.

IV. Non-Art Rejections

On page 2 of the Office Action, claims 9, 10, and 11 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regard as the invention.

At page 2, the Examiner asserts that claim 9 is indefinite for not pointing out if a specific protein is envisioned or if all proteins can be evaluated using this method. Applicants have amended claim 9 hereinabove to clarify the language of the claims and address this rejection. This amendment to the claim introduces no new matter and is supported for example by the original claim language.

At page 2, the Examiner asserts that claim 9 is indefinite for failing to define an agent and the observable signal. Applicants have amended claim 9 hereinabove to clarify the language of the claims and address this rejection. This amendment to the claim introduces no new matter and is supported for example by the specification's text at page 9, the first full paragraph.

At page 3, the Examiner asserts that claim 9 is indefinite for failing to specify the controlled stress. Applicants have amended claim 9 hereinabove to clarify the language of the claims and address this rejection. This amendment to the claim introduces no new matter and is supported for example by the specification's text at pages 6 (final paragraph) and 9 (final paragraph).

At page 3, the Examiner asserts that claim 10 is indefinite for failing to specify an amount of agitation (time, rpms). Applicants have amended claim 10 hereinabove to clarify the language of the claims and address this rejection. This amendment to the claim introduces no new matter and is supported for example by the specification's text at page 16, Table 1.

At page 3, the Examiner asserts that claim 11 is indefinite for failing to specify the type of fluorescent signal used and the amount of fluorescent signal required. Applicants amendments to the base claim from which this claim depends (claim 9) render this rejection moot. Claim 11 is therefore cancelled without prejudice and without acquiescence to the Examiner's rejection.

V. Prior Art Rejections

On page 3 of the Office Action, claims 9-16 were rejected under 35 U.S.C. §102(a) as being anticipated by Nielsen, Biochemistry, 2001, vol. 40, pp-6036-6046, "published on the web on 4/24/01" (Nielsen). On page 4 of the Office Action, claims 9-16 were rejected under 35 U.S.C. §103(a) as being unpatentable over Nielsen.

Applicants respectfully traverse these rejections for the reasons set out below.

VI. Cited References And Applicants' Invention

The Nielsen Reference

The Nielsen disclosure cited by the Examiner provides a quantitative study of the kinetics of insulin formation under different conditions using the fluorescent dye thioflavin T (ThT) as part of a search for the molecular mechanism of insulin fibrillation. The disclosure teaches that such quantitative analysis of the kinetics of fibril formation requires both well-characterized protein preparations and appropriate monitoring techniques. In this disclosure, the effect of insulin concentration, agitation, pH, ionic strength, anions, seeding, and addition of 1-anilinonaphthalene-8-sulfonic acid (ANS), urea, TMAO, sucrose, and ThT on the kinetics of fibrillation was investigated. The results of the study indicated that both nucleation and fibril growth were controlled by

hydrophobic and electrostatic interactions. Ultimately the disclosure proposes a kinetic model, involving the association of monomeric partially folded intermediates, whose concentration is stimulated by the air-water interface, leading to formation of the critical nucleus and thence fibrils.

Embodiments of Applicants' Invention

Embodiments of the invention are directed to accelerated methods of determining the relative physical stability of protein formulations. For example, independent claim 9 recites a method of evaluating the physical stability of a protein formulation by monitoring the conformational change of parallel sets of distinct protein sample formulations in response to environmental stresses (e.g. agitation). This method includes the steps of applying a survival analysis to the data obtained from the parallel protein samples and then comparing the survival analysis for each sample type to determine the relative physical stability of the protein formulations under evaluation. The recited survival curve analyses which examine the percent survival of parallel sets of native proteins (i.e. proteins in their native conformation) are similar to the analysis of data from clinical trials of pharmaceutical agents where the percent survival of a patient is compared to the survival of patients taking a placebo or another drug. See, e.g. abstract and second full paragraph on page 11.

VII. Applicants' Response To The Rejection Of Claims 9-16 Under 35 U.S.C. §102(a)

Applicants respectfully traverse the rejection because the cited reference does not teach all of the elements of Applicants' claims, for example methods which include steps such as "(e) applying a survival analysis to the data obtained for each sample type; and (f) comparing the survival analysis for each sample type to determine the relative physical stability of the protein formulations under evaluation". As noted for example at page 12 of the specification, in the method recited in claim 9, each protein formulation acts as a reference to the other protein formulations under evaluation. Thus, the relative physical stability of a series of protein formulations can be determined using survival analyses without the use of a protein reference batch. Illustrative survival analyses protocols are described in Examples 1-8 and shown in Figures 2-4 and 6-9.

A claim is anticipated only when a single prior art reference discloses each and every limitation in the claim. See, e.g., *Glaxo Inc. v. Novopharm Ltd.*, 34 USPQ2d 1565 (Fed. Cir. 1995). As

noted above, Nielsen does not teach methods of evaluating protein the physical stability of a protein formulation that apply a survival analysis to the data obtained from parallel sets of distinct protein sample formulations in response to environmental stresses (e.g. agitation), much less comparing the survival analysis for each sample type to determine the relative physical stability of the protein formulations under evaluation. Because Nielsen does not teach these elements of the claimed invention, it cannot serve as an anticipatory reference. Consequently, Applicants respectfully request the withdrawal of this rejection under 35 USC §102(a).

VIII. Applicants' Response to the Rejection of Claims 9-16 Under 35 U.S.C. §103(a)

A finding of obviousness under 35 U.S.C. §103(a) requires that all claims limitations are taught or suggested by the prior art (M.P.E.P. 2143.03). Applicants respectfully traverse the rejections under 35 U.S.C. §103(a) because the reference cited by the Examiner fails to teach or suggest methods which include steps such as "(e) applying a survival analysis to the data obtained for each sample type; and (f) comparing the survival analysis for each sample type to determine the relative physical stability of the protein formulations under evaluation". In addition, as stated in M.P.E.P. 2143.03, in order to render a claimed invention obvious, the prior art must suggest the desirability of these elements of the claimed invention. The Nielsen disclosure fails to meet this requirement for a finding of obviousness under 35 U.S.C. §103(a). In fact the Nielsen disclosure suggests the opposite by teaching artisans that quantitative analysis of the kinetics of fibril formation "requires both well-characterized protein preparations and appropriate monitoring techniques" (emphasis added). Consequently, Applicants' methods of evaluating the physical stability of protein formulations which are designed so that the relative physical stability of a series of protein formulations can be determined without the use of a well-characterized protein reference batch (see, e.g. page 12, third full paragraph) are not obvious in view of this reference.

Applicants further assert that elements such as method steps (e) and (f) in Applicants claims are not "merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan" (page 5 of the outstanding office action). Moreover, Applicants' attorney is not familiar with any art that the Examiner could rely upon to make this assertion. Consequently, absent a showing that the Nielsen reference suggests the desirability of combining the methods disclosed therein with a second disclosure that further teaches: (1) methods of applying a

survival analysis to the data obtained for each sample type; and then (2) comparing the survival analysis for each sample type to determine the relative physical stability of the protein formulations under evaluation, the above-noted legal requirements for a finding of obviousness under 35 U.S.C. §103(a) are not met. For these reasons, Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. §103(a).

Thus, Applicants submit that independent claim 9 is allowable over Nielsen. Further, dependent claims 10 and 12-16, are submitted to be allowable over Nielsen in the same manner, because they are dependent on independent claim 9, and because they contain all the limitations of the independent claim.

IX. Conclusion

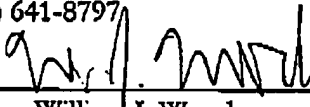
In view of the above, it is submitted that this application is now in good order for allowance and such allowance is respectfully solicited. Should the Examiner believe minor matters still remain that can be resolved in a telephone interview, the Examiner is urged to call Applicants' undersigned attorney.

Respectfully submitted,

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